Clinical Benefit for New Drug Approvals

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Outline

1. New drug approval standards at FDA:
    a. definition of clinical benefit
    b. surrogates of clinical benefit

2. Examples of the use of subclinical or minimal residual disease (MRD) as endpoint for drug approval at FDA
    a. ↓ viral load for anti-HIV drug approvals
    b. ↓ Bcr-Abl mRNA level for approval of Tasigna in CML

Basis for New Drug Approval by FDA

- Demonstration of efficacy and acceptable safety by adequate and well-controlled trials (505(d) FDCA)

- Ability to generate product labeling that:
  - Defines an appropriate patient population for treatment with the drug
  - Provides adequate information to enable safe and effective use (prescribing) of the drug

- Analogous rules apply to Biologics

Approval Types

- Regular approval – substantial evidence of clinical benefit demonstrated prior to approval based on prolongation of life, a better life or an established surrogate for either of the above (505(d) FDCA)

- Accelerated approval designed to hasten the delivery of products appearing to provide substantial evidence using a surrogate for benefit for serious or life-threatening illnesses lacking satisfactory treatments. (21 CFR 314.510)

Accelerated Approval

- "Surrogate endpoint reasonably likely… to predict clinical benefit"
- "Serious or life-threatening illness"
- "Meaningful therapeutic benefit to patients over existing treatments…"
- Confirmatory trial "requirement … to verify and describe its clinical benefit."
  - Must be "adequate and well-controlled", carried out with "due diligence" and are usually underway at the time accelerated approval is granted.
    - 21 CFR 314.510 and 21 CFR 601.41

Regulatory Flexibility

- Wide range of drugs and their usage demand flexibility in applying the statutory standards
- FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards
- To apply this flexibility, FDA provides guidance to sponsors during drug development

21 CFR 314.105

Example 1: Anti-HIV Drugs

Sub-clinical disease (as measured by viral load or MRD) as regulatory endpoint

HIV Drug Approval: 1991

- Endpoint to show benefit for approval:
    a. CD4 cell level
    b. p24 viral antigen

- Patients forced to watch their p24 viral antigen level increase until CD4 cell level declined

RT-PCR for Plasma HIV RNA as Highly Predictive for Benefit: 1996

- Surrogate Marker Working Group (industry, academia, NIH and FDA) worked together to test for correlations in 5000 patients between clinical outcome and post therapy reduction of viral load as measured by plasma HIV RNA by RT-PCR

- This effort showed that short-term viral load suppression (≤ 50 transcripts/ml plasma) after therapy positively correlated with durability of viral load response, and risk of clinical progression and death

HIV Drug Approval: 1996 to Present

- Real-time RT-PCR monitoring of viral load level became standard in 1996
- Decision to change drugs occurred prior to decline of CD4 level or clinical progression
- Antiviral Advisory Committee in 1997
  - ↓ HIV RNA endpoint at 24 weeks: Accelerated approval
  - ↓ HIV RNA endpoint at 48 weeks: Regular approval
  - Concordance with CD4 cell levels
- Currently RT-PCR for ↓ plasma HIV RNA is used as regulatory endpoint and for clinical decision making

Example 2:
Tyrosine Kinase Inhibitors for CML

Sub-clinical disease (as measured by leukemia specific mRNA in WBC or MRD) as regulatory endpoint

Harmonization of Methodology for Detection of Bcr-Abl Transcripts

- EAC* Program to Standardize RT-PCR in 2003
- Consensus Meeting at NIH in 2005
  - RNA quality
  - RT-PCR methodology
  - Control genes
  - Quality assurance of assay
  - International reference and control material
  - Expression of results on international scale

*EAC=Europe Against Cancer;

Gabert et al Leukemia 17: 2318, 2003; van der Velden et al Leukemia 17: 1013, 2003; Hughes et al NEJM 349:1423, 2003; Hughes et al Blood 108: 28-37, 2006

IRIS Trial

- Study of 1106 newly diagnosed CML-CP randomized to interferon-alpha (target dose of 5 million U/m^2 sc qd) with cytarabine (20 mg/m^2 sc qd X10 every 28 d) vs imatinib (400 mg po qd)

- Primary Endpoint: Progression (death, AP, loss of CHR)
- Secondary Endpoints: CHR, CCyR or pCyR

- Exploratory Goal: to determine the prognostic value of measuring at a sub-clinical level the disease burden by Bcr-Abl RT-PCR in patients with CMP who have achieved a CCyR

Standardization of RT-PCR for Bcr-Abl mRNA for IRIS Trial

- Bcr-Abl values expressed as a percentage of Bcr (or Abl) transcript levels to compensate for variations in RNA quality and differences in RT-PCR reaction efficiency
- The median value of Bcr-Abl/Bcr ratio of 30 samples from patients with chronic phase CML were used as standardized baseline at each of 3 laboratories
- The reduction in Bcr-Abl/Bcr ratio after therapy as compared to the standardized baseline was calculated for each sample and shown as $\log_{10}$ (3 log reduction=MMR)

Gabert et al Leukemia 17: 2318, 2003; van der Velden et al Leukemia 17: 1013, 2003; Hughes et al NEJM 349:1423, 2003

IRIS Trial: Results at 1 year

Real-time quantitative RT-PCR used to measure Bcr-Abl/Bcr ratios at Baseline and at pre-specified times after treatment

Results at 1 year:	Imatinib	Interferon/cytarabine
CCyR in all patients	68%	7%
MMR in all patients	39%	2%

*CCyR=complete cytogenetic response;

Hughes et al NEJM 349: 1423, 2003

IRIS Trial Results at 7 Years

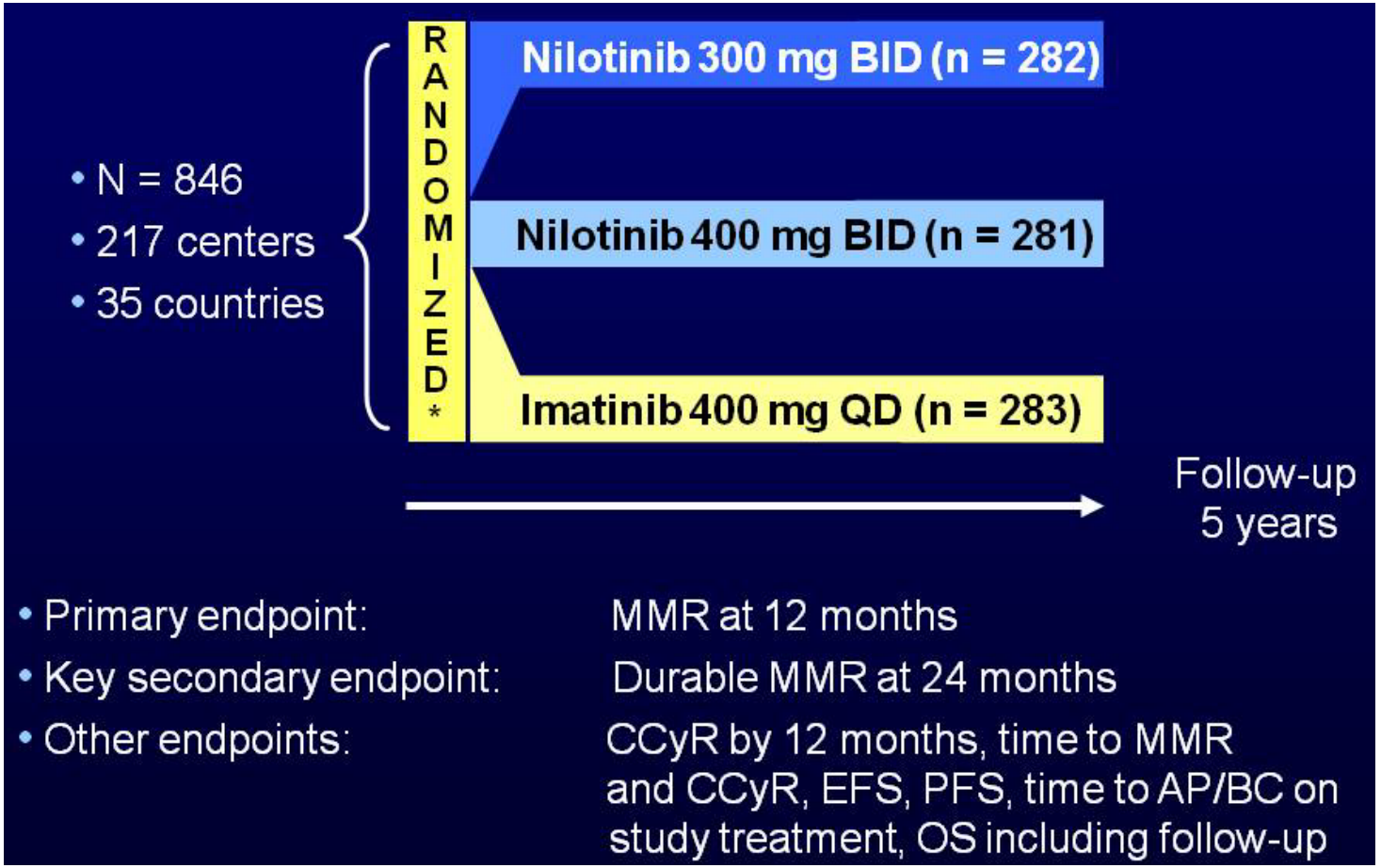
- Does the sub-clinical disease (as measured by MMR status) at 18 months correlate with: 1) percent remaining in CCyR at 7 years, and 2) overall survival?

Percent	Loss CCyR (7yrs)	OS Rate (7yrs)
MMR^+ at 18 months	3%	90.3%
MMR^- at 18 months	26%	89.0%
P value	<0.001	NS

- MMR status at 18 months correlates with CCyR status but not of OS at 7 years

Hughes et al Blood 116: 3758, 2010

MMR as Primary Endpoint in Pivotal Trial for Treatment Naïve CML



Saglio G et al. NEJM, 362: 2251, 2010

Trial Results: Accelerated Approval of Nilotinib (Tasigna) for CML-CP

Primary Endpoint:	Tasigna*	Imatinib*	P value**
MMR at 12 mos	44%	22%	<0.001
CCyR by 12 mos	80%	65%	<0.001

*Tasigna at 400 mg po bid vs Imatinib at 400mg po qd;

**CMH test stratified by Sokal risk group

- Tasigna (300 mg po bid) vs Imatinib (400 mg po qd) was also significant at P<0.0001.

Conclusions: Steps for Development of MRD as Regulatory Endpoint

1. Identify MRD endpoint in clinical trials
2. Develop assay for MRD
3. Harmonization (Consensus Conference)
4. Standardization of assay for MRD
5. Apply standardized assay prospectively
6. Apply MRD assay to regulatory action